

### **REMARKS**

Claims 1 and 17 have been amended, claims 4-6 and 19-21 cancelled in view of these amendments.

In particular, claims 1 and 17 have been amended to recite that the plant material is protonema tissue selected from the group consisting of *Physcomitrella patens*, *Marchantia polymorpha*, *Ceratodon purpureus*, and *Funaria hygrometica*.

Claim 17 is amended to recite “photosynthetically-active” plant material, as supported by, *e.g.*, page 6, lines 27-29.

The wording in claims 1 and 17 has also been rearranged for improved readability, and not for any reason related to patentability nor to change the scope of the claims.

No new matter has been added to the present application by the amendment.

### **The Rejections**

Claims 1-6, 17, and 20-21 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement.

Claims 1-5, 17 and 19-21 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Reutter (Plant Tissue Culture and Biotechnol. 2:142-147, 1996) [hereinafter “Reutter”] in view of Lee et al. (U.S. Patent No. 6,020,169) [hereinafter “Lee”].

Claims 6 and 21 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Reutter in view of Lee and in further view of Nasu et al. (M. Nasu et al., 84 J. Ferm. Bioeng. 519: 519-523 (1997)) (hereinafter, “Nasu”).

In view of the present amendment, Applicants respectfully traverse the rejection and request reconsideration for the following reasons.

## **APPLICANTS' ARGUMENTS**

### **THE REJECTION UNDER 35 U.S.C. § 112 IS UNTENABLE**

#### **A. The Rejection Under § 112 is Untenable in View of the Amendment to the Claims**

Each of the independent claims is now limited to protonema tissue selected from the group consisting of *Physcomitrella patens*, *Marchantia polymorpha*, *Ceratodon purpureus*, and *Funaria hygrometica*, so that those of ordinary skill in the art are unquestionably able to make and use the full scope of the claimed invention without undue experimentation. Empirical evidence of record shows that the procedures described in the specification enable one of ordinary skill in the art to practice the claimed invention on these four species. In particular, the examples in the specification amply demonstrates enablement in *Physcomitrella patens* (as acknowledged by the Examiner, who did not make an enablement rejection against claim 19 which was limited to this species, and further has admitted that the application is enabled for a method for the production of *Physcomitrella patens* by transformation with constructs that encode signal peptides operably linked to the proteins (Office Action dated March 14, 2006, at 2, lines 9-12)). Moreover, the Gorr Declaration filed on December 7, 2005 [hereinafter “the Gorr Declaration”], paragraphs 14-23, using the methods of the original disclosure of this application, demonstrated that *Funaria hygrometica* and *Marchantia polymorpha* could be transformed and are fully enabled. Furthermore, the Examiner admits that *Ceratodon purpureus* and *Marchantia polymorpha* had been transformed as of the filing date of the present application (Office Action dated January 18, 2007, page 3, lines 22-23): from transformation, one of skill in the art could rely on the specification and no more than routine experimentation in order to obtain secreted heterologous proteinaceous substances from the culture medium based on the disclosure of the present invention. All of this, combined with the expert opinions of the Gorr Declaration and the Reski Declaration filed October 13, 2006, as discussed extensively in the response filed the same day, amply demonstrate that the invention is enabled for the four species *Physcomitrella patens*, *Marchantia polymorpha*, *Ceratodon purpureus*, and *Funaria hygrometica* presently claimed, and Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112.

B. Even Without the Claim Amendment, the Examiner's Arguments Lack Foundation

The Examiner presents three points in support of the enablement rejection.

First, the Examiner notes that no reports of transformation of other moss or liverwort species appear in the post-filing art, despite the “extraordinary ability of *P. patens* to be transformed,” suggesting that this is because such transformation is difficult. On the contrary, investigators have no motivation to develop another model but instead could use *P. patens*, whose possibilities for functional gene analysis far exceed those of the *Arabidopsis* and tobacco model organisms used hitherto. Since experts in the field have already worked with this moss species for a long time and have compiled very extensive data material including an extensive EST data bank, naturally they do not need a further representative of the bryophytes and are therefore concentrating their research completely on *Physcomitrella patens*. Lack of research activity towards other species carries no weight towards the enablement of these species. Why should research laboratories use their resources for other species, when an excellent model organism is already available? This would simply be a waste of money and personnel.

Second, the Examiner cites a statement by the co-inventor Reski (1998, Bot. Acta 111:1-15) that “there has been a serious delay on [sic] the use of new techniques of plant molecular biology [on moss species], and molecular analysis [sic] have concentrated on *Physcomitrella*.” This is disingenuous. The full quotation is as follows:

Although a wealth of physiological data have been accumulated for different moss species, there has been a serious delay in the use of new techniques of plant molecular biology and the molecular analyses have concentrated on *Physcomitrella*, a species with a genome size of about three times that of *Arabidopsis* (480 Mbp; Gorr and Reski. 1997), distributed on n= 27 chromosomes (Reski et al., 1994).

It is apparent from this full quote that it refers to the actual use of these techniques, not to the actual ability of such techniques to be used (enablement).

Third, the Examiner states that the Applicants and their collaborators have not published relating to this invention in other than *Physcomitrella*, suggesting either actual lack of enablement or perceived lack of enablement on the part of reviewers. However, common sense rejects a superfluous waste of research resources, which may be better spent optimizing conditions for use of *Physcomitrella patens*. Again, as with the first point, lack of research activity towards other species carries no weight towards the enablement of these species.

**THE REJECTION UNDER 35 U.S.C. § 103(a) IS UNTENABLE**

None of the cited references teach, or even suggest, obtaining secreted heterologous proteinaceous substances from intact protonema tissue, which is a multicellular differentiated plant tissue that is photosynthetically active.

Lee et al. describes the isolation of a biologically active heterologous protein from single tobacco cells held in suspension culture (col. 12, lines 6-9 and 48-49). However, it is known that single-cell cultures of tobacco cells are permeable to proteins at least as large as 150 kDa (see Raskin, U.S. Patent 6,096,546, col. 2, lines 5-10). Lee estimates the size limit to be about 50 kDa or higher (col. 6, line 29). Thus, Lee does nothing to show the obviousness of the surprising and unexpected result of the present invention, namely obtaining secreted proteins from the media of protonema cultures, which are photosynthetically active multicellular and differentiated tissue.

Mosses do not belong to the higher plants that have vascular systems, and therefore the two are not comparable, and the combination of Lee with Reutter is inappropriate. The Lee reference does not in fact consider that mosses and liverworts are “plants,” noting that: “[t]he term ‘plant; encompasses any higher plant and progeny thereof, including monocots (e.g., rice), dicots (e.g., tobacco, Arabidopsis, carrot, etc.), gymnosperms, etc.” (col. 8, lines 49-51). The mosses do not belong to the higher plants such as, *e.g.*, tobacco. Even different types of single cells held in culture cannot easily be compared with one another, much less multicellular protonema culture, as far as their properties and in particular their cell wall morphology are concerned.

Furthermore, the Lee reference teaches away from the combination made by the Examiner. Lee states that “[p]lant suspension culture systems provide significant advantages over protein production in intact transgenic plants, which requires cultivation, harvesting and expensive extraction procedures to obtain non-secreted foreign proteins” (col. 4, lines 34-38). However, the claimed invention relates to such “intact transgenic plants.” One of ordinary skill in the art would have to assume that desired heterologous proteins, when using complete plants, can only be secreted directly into the apoplastic space, but not into the medium.

Moreover, Lee has the non-photosynthetically active (heterotrophic) tobacco cells supplemented with 3% sucrose, which must serve as a carbon source (nutrient) (col. 12, lines and 48-49), whereas the species of the current claims are phototrophic (capable of photosynthesis). None of the prior art documents show secretion of heterologous proteins through the cell wall of photosynthetically active tissue of a plant without disruption of the cell wall.


For all of the above reasons, the combination of Reutter with Lee is untenable as against the present claims, and Applicants respectfully request reconsideration and withdrawal of the rejections under § 103.

## CONCLUSION

For all of the above reasons, claims 1-3 and 17 are in condition for allowance, and a prompt notice of allowance is earnestly solicited.

Questions are welcomed by the below-signed attorney for applicants.

Respectfully submitted,  
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